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This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c).

Express Mail Label No. EL

INVENTOR(S)		
Given Name (first and middle [if any])	Family Name or Surname	Residence (City and either State or Foreign Country)
Ali	Rezai, et al.	Bratenahl, OH

☐ Additional inventors are being named on the ___ separately numbered sheets attached hereto

TITLE OF THE INVENTION (280 characters max)

Neurostimulation For the Treatment of a variety of conditions, including chronic pain syndromes, hypothalamic related disorders, sleep disorders, and stroke

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ENCLOSED APPLICATION PARTS (check all that apply)

☑ Specification	Number of Pages 31	☐ CD(s), Number	
☑ Drawing(s)	Number of Sheets (included above)	☑ Other (specify)	Certificate of Express Mail Postcard
☐ Application Data Sheet. See 37 CFR 1.76			

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Respectfully submitted,

SIGNATURE _____ Date 2/1/02

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USE ONLY FOR FILING A PROVISIONAL APPLICATION FOR PATENT

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NEUROSTIMULATION FOR THE TREATMENT OF A VARIETY OF CONDITIONS, INCLUDING CHRONIC PAIN SYNDROMES, HYPOTHALAMIC-RELATED DISORDERS, SLEEP DISORDERS, AND STROKE

BACKGROUND

The use of neurostimulation (including deep brain stimulation, limbic stimulation, and modulation of neural structures for both the excitation and inhibition of the neural elements) provides an effective alternative to today's surgical lesioning techniques in the treatment of chronic pain syndroms, disorders linked to hypothalamic neural elements, sleep disorders and stroke. While technologically improved and more precise, today's surgical lesioning techniques have the fundamental limitation of being inherently irreversible and are essentially a "one shot" procedure with little chance of alleviating or preventing potential side effects. In addition, there is a limited possibility to provide continuous benefits as the disorder progresses and the patient's symptoms evolve.

It has been recognized that electrical stimulation holds significant advantages over lesioning in the treatment of various disorders, inasmuch as lesioning can only destroy nervous system tissue. In many instances, the preferred effect is to stimulate to increase, decrease, or block neuronal activity. Electrical stimulation permits such modulation of the target neural structures and, equally importantly, does not require the destruction of nervous tissue. In many ways, this is analogous to a reversible and adjustable lesioning procedure.

The hypothalamus is a central neurological structure composed of over 10 sub-components which control a wide array of functions of the human body. The hypothalamus is one of the most primitive but essential structures within the brain. Its core functions include homeostasis (including maintenance of body temperature, body fluid status, blood pressure, etc.) as well as regulation of various hormones released from the hypothalamus and the hypothalamic-pituitary axis. In addition, basic human activity such as anger, sexual drive, fear, appetite, etc are controlled via the hypothalamus. Furthermore, the regulation of female ovulation is controlled by the hypothalamus.

It is known that the limbic structures are associated with the emotional and memory components of chronic pain syndromes, including neuropathic pain, complex regional pain syndrome I or II, cancer pain, failed back surgery syndrome, phantom limb pain, etc. This is an even more particular problem because a significant component of chronic pain includes the memory of pain which is not forgotten even after treatment for the pain has been initiated.

It is believed that up to 20% of the general population has sleep disorders. Sleep disorders can include Narcolepsy and its clinical manifestations such as sleep attacks, cataplexy, sleep paralysis, hypnagogic hallucinations insomnia, sleep apnea, hypersomnia and related disorders. Narcolepsy is a particularly dangerous problem given its incidence of 0.05% (Data from American Association of Sleeping Disorders).

Sleep is an active process during which many body functions fluctuate, including respiration, temperature, body tone and hormone secretion. A specialized type of sleep, Rapid Eye Movement (REM sleep) is associated with dreaming, fleeting eye movements, muscle twitching, a generalized decrease in body tone, and irregular respiration, heart beat and blood pressure.

The most notable disorder resulting from impaired CNS control of wakefulness and the sleep/wake cycle is narcolepsy. This disorder is characterized by the intrusion of REM sleep into the waking state or into the transition periods between waking and sleep. Many narcoleptics are sleepy during most or all of the day, specifically during times when normal people may only have a tendency to become somnolent. An example would be the tendency of a normal person to become somnolent after a heavy meal which the Narcoleptic would fall asleep.

Patients with narcolepsy are subject to narcoleptic sleep attacks, cataplexy, sleep paralysis and hypnagogic hallucinations; however, an individual patient may not have all these symptoms. Sleep attacks may occur at any time the day and in embarrassing and dangerous situation, such as while walking, climbing, ladder or even driving. Cataplexy is characterized by loss of body tone without loss of consciousness. These attacks are brief but can occur anytime and in any situation. Sleep paralysis is the loss of tone, as occurs during an episode of REM sleep, but when the patient is awake. Its consequences are relevant and extremely dangerous.

The causes for those sleep disorders is the sudden intrusion of the REM sleep during awake period. The rationale is this situation is to abort the REM sleep, modulating specific nuclei in the brain stem. Several papers highlight the role of Locus Coeruleus in the generation of REM Sleep. The inhibition of this specific nucleus in experimental trials interrupt the REM Sleep and its clinical manifestations, controlling and avoiding the dangerous consequences of those sleep disorders. The same neurophysiological response happens when lesion

This small noradrenergic nucleus (Locus coeruleus) and the Nucleus Reticularis Pontis Oralis and Caudalis (NRPO and NRPOC) has been pointed in several paper as the main relay for the generation of REM sleep. (Jouvet, 1972, Ward and Gunn, 1976, Swanson, 1976).

Stroke is a major medical problem facing this country and the world. With a rapidly aging population, the incidence of stroke is increasing. Stroke is the #1 cause of serious, long-term adult disability in the United States and the third leading cause of death after heart disease and cancer. It kills nearly 160,000 people each year. Every 45 seconds someone in the U.S. will experience a stroke. Every year, more than 750,000 Americans have a new or recurrent stroke. Over the course of a lifetime, four out of every five American families will be touched by stroke. 4,000,000 Americans are living with the effects of stroke. About 1/3 have mild impairments, another third are moderately impaired and the remainder are severely impaired. Approximately one third of younger individuals with stroke and three quarters of older individuals with stroke have persisting impairments and disabilities.

It has been estimated that one in three stroke survivors need help caring for themselves, one in five need help walking and seven out of ten cannot return to their previous jobs.[5] 51% are unable to return to any type of work after stroke.

Stroke costs the U.S. $30 billion dollars annually in medical expenses and lost productivity. Given this enormous impact on the health care, there are few options to help patients regain function after a stroke. Patients can undergo aggressive rehabilitation to improve function and usually plateau in their functional improvement after one year. The current method will enable patients to have improved functioning beyond the currently available methods.

SUMMARY OF THE INVENTION

Surgical treatments for hypothalamic-related, sleep, chronic pain disorders and stroke described above that have traditionally been treated by behavioral therapy or drugs, have been largely limited to the stereotactic lesioning such as cingulotomy, capsulotomy, subcaudate tractotomy, and limbic leucotomy. Such procedures have been applied to date in the treatment of affective disorders and anxiety disorders. If one critically examines the results of these procedures in the literature, it becomes apparent, when applied to a carefully selected patient population in conjunction with modern stereotactic surgical equipment and imaging techniques, that these procedures are both efficacious and safe. In fact, in a certain subset of patients who have failed all conventional treatments, these neurosurgical procedures may be the only treatment options available. Therefore, electrical and/or chemical neurosurgical neuromodulating techniques, with their inherent reversibility and adjustability, offer a safer and potentially more effective alternative to lesioning procedures.

The present invention finds particular utility in its application to disorders manifesting in humans. However, it is also to be appreciated that the present invention is applicable to other animals which exhibit behavior that is modulated by the brain. This may include, for example, primates, canines, felines, elephants, dolphins, etc. Utilizing the various embodiments of the present invention, one skilled in the art may be able to modulate the functional outcome of the brain to achieve a desirable result.

One technique that offers the ability to affect neuronal function in a reversible and dynamic fashion is the delivery of electrical stimulation for neuromodulation directly to target tissues via an implanted electrode assembly.

Another technique that offers the ability to affect neuronal function in a reversible and dynamic fashion is the delivery of drugs or neuromodulating chemicals directly to target tissues via a subcutaneously implanted pump and/or a slow release matrix. Such drugs, either traditional disorder-treating agents or chemicals mimicking neurotransmitters, could be instilled precisely at such low doses as to completely avoid the side effects so common to modern pharmacotherapy and to provide a physiological neuromodulation. Such doses could also be tailored in magnitude

with respect to a particular patient's varying symptomatology. A chemical neuromodulating system may also be implanted as a primary treatment strategy or in combination with an electrically based one.

A combination therapeutic approach, one combining electrical and chemical means, would be penultimate to generating healthy neuronal tissue itself. In addition to the stimulation and chemical modulation, the implantable device could also have chemical and/or electrical sensing functions that can be coupled to the chemical and electrical output of the modulating device.

Initially there is an impetus to treat hypothalamic-related, chronic pain, sleep disorders and stroke with direct modulation of activity in that portion of the brain causing the disorder. In this regard there have been a number of studies that have helped to identify the neural structures and their precise connections which are implicated in causing these disorders. These are the structures that are functioning abnormally and manifesting in the particular disorder. Numerous anatomical studies from autopsies, animal studies, and imaging such as computerized tomography (CT) scans, and magnetic resonance imaging (MRI) scans have demonstrated the role of these structures and their connections in psychiatric activity/disorders. In addition to these anatomical studies, a number of physiological techniques and diagnostic tools are used to determine the physiological aberrations underlying these disorders. This includes electrical methods such as electroencephalography (EEG), magnetoencephalography (MEG), as well as metabolic and blood flow studies such as functional magnetic resonance imaging (fMRI), and positron emission tomography (PET). The combination of the anatomical and physiological studies have provided increased insight into our understanding of the structures which are involved in the normal functioning or activity of the brain and the abnormal functioning manifesting in these disorders.

One embodiment of the present invention relates generally to modulating the pathological electrical and chemical activity of the brain by electrical stimulation and/or direct placement of neuromodulating chemicals within the corresponding areas of abnormal function and activity. In accordance with this embodiment of the present invention, a method is provided which provides

surgical treatment of disorders by implantation of stimulating electrodes and/or drug/chemical delivery micro infusion at the locations detailed herein.

In one embodiment of the invention, therefore, the proximal end of the electrode and/or catheter is coupled to an electrical signal source and/or drug delivery pump which, in turn, is operated to stimulate the predetermined treatment site in regions described above such that the functional outcome is achieve or the clinical effects of the psychiatric and disorders are reduced.

In an another embodiment of the present invention, a method of determining the proper therapeutic treatment (i.e., the proper position or placement of the electrodes and/or catheters) for a specific disorder comprising the steps of: identifying a large sampling of patients (each exhibiting a common disorder) and then identifying which common region of the brain exhibits pathological electrical and/or chemical activity during manifestations of the specific disorder. The common regions demonstrating this pathological activity constitute the predetermined treatment site, wherefore a suitable means for affecting the activity of said predetermined treatment site may be employed to ameliorate/improve the disorder generically with a high probability of success.

In particular, the common regions identified with respect to the disorders discussed herein, are herein identified by their known anatomical connections and physiological functioning as being actively involved in channeling or generating the pathological electrical activity associated with the disorders. It is important to note that these regions, including their functions and connections, are a common structural feature of human brains, and therefore is a common target across a large number of patients. As suggested above, this commonality of function and structure in these structures implicated in the disorder allows for common treatment targeting, even in instances wherein different patients have other disparate locations within their brains that also exhibit pathological electrical and/or metabolic activity.

Sleep Disorders

The invention includes a description of a method for the use of neurostimulation device in order to treat sleep disorders. More specifically, we are identifying the Locus Coeruleus and other correlated nuclei (Dorsal Raphe Nucleus, Posterior Hypothalamus, Nucleus Reticularis

Pontis Oralis and Caudalis, Basal Forebrain) as possible stereotactic targets for the treatment of sleep disorders. The nucleus (Locus Coeruleus) is located in the posterior portion of the brainstem, close to the fourth ventricle and can be reached using conventional stereotactic functional neurosurgical methods. In one embodiment of this invention, stimulation of the Locus Coeruleus can also be performed in order to re-establish a normal awakeness-sleep cycle. Also, this application can be utilized to treat patients with severe jet lag phenomenon.

Similarily, any of the related nuclei in the circuitry of sleep may also be modulated to achieve a desired effect to treat any of the above disorders.

Modulation of the Locus Coeruleus and the related nuclei can include electrical stimulation or inhibition or chemical modulation via an infusion system.

In another embodiment of this invention, the cortical or subcortical sensors can monitor the brain's sleep rhythms in order to allow for a closed-loop feedback and autoregulation of the system. Further sensory monitors can also include internal or external vital sign monitors for heart rate, respiration, REM, body tone, etc. An example of this latter description includes a system for Narcolepsy which would monitor the brain's sleep rhythm and result in inhibition of the Locus Coeruleus if it was detected that the brain was approaching REM sleep. Of course this system would be programmed to be in an off mode at night to encourage physiological sleep.

The stereotactic coordinates for the several nuclei, relative to the AC-PC Line, are as follows:

Locus Coeruleus
Axis X (Medial-lateral): 0 to 6mm from Mid AC-PC line
Axis Y (Antero-Posterior): 5-9 mm Posterior to PC
Axis Z (Dorsal-Ventral): 7-17mm from Mid AC-PC line

Dorsal Raphe
Axis X (Medial-lateral): 0 to 8mm from Mid AC-PC line
Axis Y (Antero-Posterior): 3-9 mm Posterior to PC
Axis Z (Dorsal-Ventral): 2-10mm from Mid AC-PC line

Nucleus Reticulares pontis oralis/caudalis

Axis X (Medial-lateral): 0 to 6mm from Mid AC-PC line

Axis Y (Antero-Posterior): 2-8 mm Posterior to PC

Axis Z (Dorsal-Ventral): 5-22mm from Mid AC-PC line

Posterior Hypothalamus

Axis X (Medial-lateral): 0 to 6mm from Mid AC-PC line

Axis Y (Antero-Posterior): 8-14 mm Posterior to AC

Axis Z (Dorsal-Ventral): 0-8mm from Mid AC-PC line

Basal Forebrain

Axis X (Medial-lateral): 0 to 20mm from Mid AC-PC line

Axis Y (Antero-Posterior): 0-36 mm Anterior to AC

Axis Z (Dorsal-Ventral): 0-25mm from Mid AC-PC line

The electrode system will include a cannula which can redirect the electrode in a direction to allow maximal coverage of the locus coeruleus. Also the impulse generator must include an internal synchronizable clock which can be externally programmed via telemetry in order to resynchronize sleep patterns.

Chronic Pain Syndrome

The neurostimulation methods, techniques and devices described herein may also be used for the treatment of chronic pain syndromes including neuropathic pain, complex regional pain syndrome I or II, cancer pain, failed back surgery syndrome, phantom limb pain, etc. This is an even more particular problem because a significant component of chronic pain includes the memory of pain which is not forgotten even after treatment for the pain has been initiated. It has been previously known that the limbic structures deal with these emotional and memory

components. Modulation of the limbic structure or structures will be able to affect this. In addition, the current system will employ the ability to allow for chemical modulation, and remote sensing as well as closed-loop feedback capabilities. Additionally, any of the anatomical areas involved in the pain circuitry as described in the figures can be utilized to modulate the pain response. Alternatively, the pain circuit is much more complex and has many other components involved within its circuitry. DBS can reliably modulate any one or combination of these CNS sites.

Hypothalamic-Related Disorders

The hypothalamus is a central neurological structure composed of over 10 sub-components which control a wide array of neurological and other physiological functions of the human body. The hypothalamus is one of the most primitive but essential structures within the brain. Its core functions include homeostasis (including maintenance of body temperature, body fluid status, blood pressure, etc.) as well as regulation of various hormones released from the hypothalamus and the hypothalamic-pituitary axis. In addition, basic human activity such as anger, sexual drive, fear, appetite, etc are controlled via the hypothalamus. Furthermore, the regulation of female ovulation is controlled by the hypothalamus. Deep brain stimulation can be utilized to modulate the above functions of the hypothalamus by targetting the different nucleus (nucleii) or neural elements in the hypothalamus either via electrical or chemical modulation to effect the mentioned functions. In another aspect of this invention, modulation of the hypothalamic associated circuitry effects can also be accomplished with sensing and modulation of both the hypothalamus and any other aspect within the circuitry. The figures attached hereto describe the disorders linked to different hypothalamic neural elements together with the hypothalamic regions and their functions.

Still further aspects of the present invention will become apparent to those of ordinary skill in the art upon reading and understanding the following detailed description of the preferred embodiments.

Stroke

An embodiment of the present invention involves the use of neurostimulation for the treatment of patients with stroke. A number of studies have demonstrated neuroprotective effects of brain and spinal cord stimulation in animal models and human. Spinal cord stimulation has also been shown to be beneficial for patients with angina as well as improving cerebral blood flow in patients with stroke. The mechanisms can involve neuroprotection of the ischemic tissue via activation, inhibition or modulation of neuronal elements in the involved tissue, adjacent or at a distant site. This can involve the modulation of various inhibitory and/or excitatory neurotransmitters implicated in the region of the stroke, adjacent tissue or distant site. An additional mechanism may involve the increase or modulation of cerebral blood flow to the involved or adjacent tissue. Furthermore, induction of plasticity in the adjacent tissue of a stroke is seen in the acute and chronic stage and stimulation can potentially induce further plasticity. Berger and Yamamoto have shown that stimulation of sub-cortical deep cerebellar (fastigial) as well as the subthalamic nuclei can result in protection against ischemic event. This protection can be explained by increased blood flow as well as other mechanisms that are not fully understood.

An embodiment of the current invention proposes stimulation of the involved ischemic area, the adjacent area or distant site that has connections to the ischemic area or adjacent area.

The ischemic area may be secondary to a thrombotic or stenotic phenomenon or related to a hemorraghic event. The stimulation can be intraparenchymal, on the cortex, subdural, epidural or on the skin surface. Currently available neuromodulation electrodes can be used or a custom design being a cylindrical, ovoid, plate or grid like electrode. The stimulation parameters include monopolar, bipolar or multipolar, intensities of 0.1 μV to about 20 V intensity, frequency off 2 Hz to about 2500 Hz, pulse width of 10 microseconds to about 1,000 microseconds.

A grid electrode of different size and shapes which can remain supracortically with the option of one or more intracranial extensions is proposed to allow for the delivery of electrical stimulation.

Additionally, stimulation of deep brain nuclei such as the fastigial nucleus of the cerebellum and the vasodilator area of the subthlamic nucleus or any of the brain areas associated with vasodilation could be performed for a patient with cerebral ischemia symptoms.

Additional use of microinfusion of chemicals is also incorporated into the device to allow for the infusion of vasodilatary or vasoconstrictive medications such as nitric oxide, nitroprusside, hydralazine, dopamine, antithrombotic agents or thrombotic agents, and/or cerebral protective agents.

Additionally, in still another embodiment with pH probes, detection of bleeding parameters, and oximetry systems will be incorporated to the electrode device to optimally alter the delivery of the modulater(electric or chemical) in a closed-loop manner.

Although the invention has been described with reference to the preferred embodiments, it will be apparent to one skilled in the art that variations and modifications are contemplated within the spirit and scope of the invention. The drawings and description of the preferred embodiments are made by way of example rather than to limit the scope of the invention, and it is intended to cover within the spirit and scope of the invention all such changes and modifications.

We claim:

1. A method as shown and described.
2. An apparatus as shown and described.

DESCRIPTION OF THE DRAWINGS

The invention may take form in various components and arrangements of components and in various steps and arrangements of steps. The drawings are only for purposes of illustrating the preferred embodiments and are not to be construed as limiting the invention.

Fig.1 and shows the noradrenergic connections of the Locus Coeruleus in the several central nervous system relay envolved in the regulation of the awakefulness-sleep cycle. LC: locus coeruleus. RF:Dorsal raphe nucleus. T: Thalamus. H: Posterior hypothalamus. CTX: Cortex.

Fig. 2 shows the medial surface of the brain.

Figure 3: Limbic circuitry involved in pain

Figure 4: Prior cingulotomy

Figure 5: Other area in the brain where lesions have been performed for pain control.

Figure 6: Pain circuitry

Figure 7: Electrode in brain

Table 1: Coordinates for limbic structures

Table 2: Diseases Linked to Different Hypothalamic Neural Elements

Table 3: Hypothalamic regions and their Functions

Figure 8: Electrode in Brain

Figure 9: A CT Scan (A) , MRI T1 (B) and T2 (C) (Clockwise from top left) of the brain revealing a left parietal stroke.

Figure 10: A craniectomy has been performed and a grey electrode lies epidurally over the region of the stroke (A)

Figure 11: CT Scan of a large right hemispheric stroke with craniectomy electrode. (Different example than in Figures 9-10).

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21. Yamamoto S, Golanov E. Reductions in Focal Ischemic Infarctions Elicited from Cerebellar fastigial Nucleus

FIGURE 1

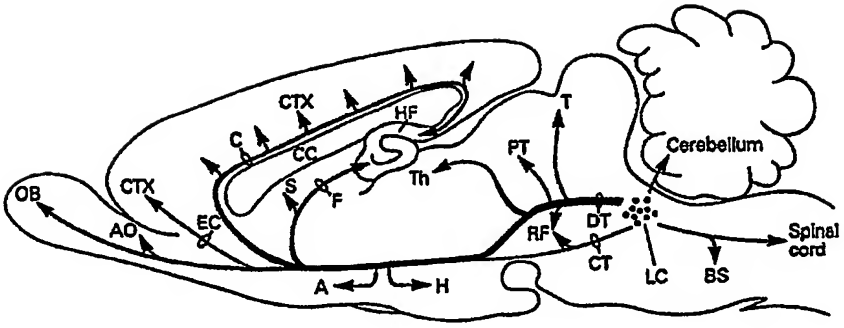
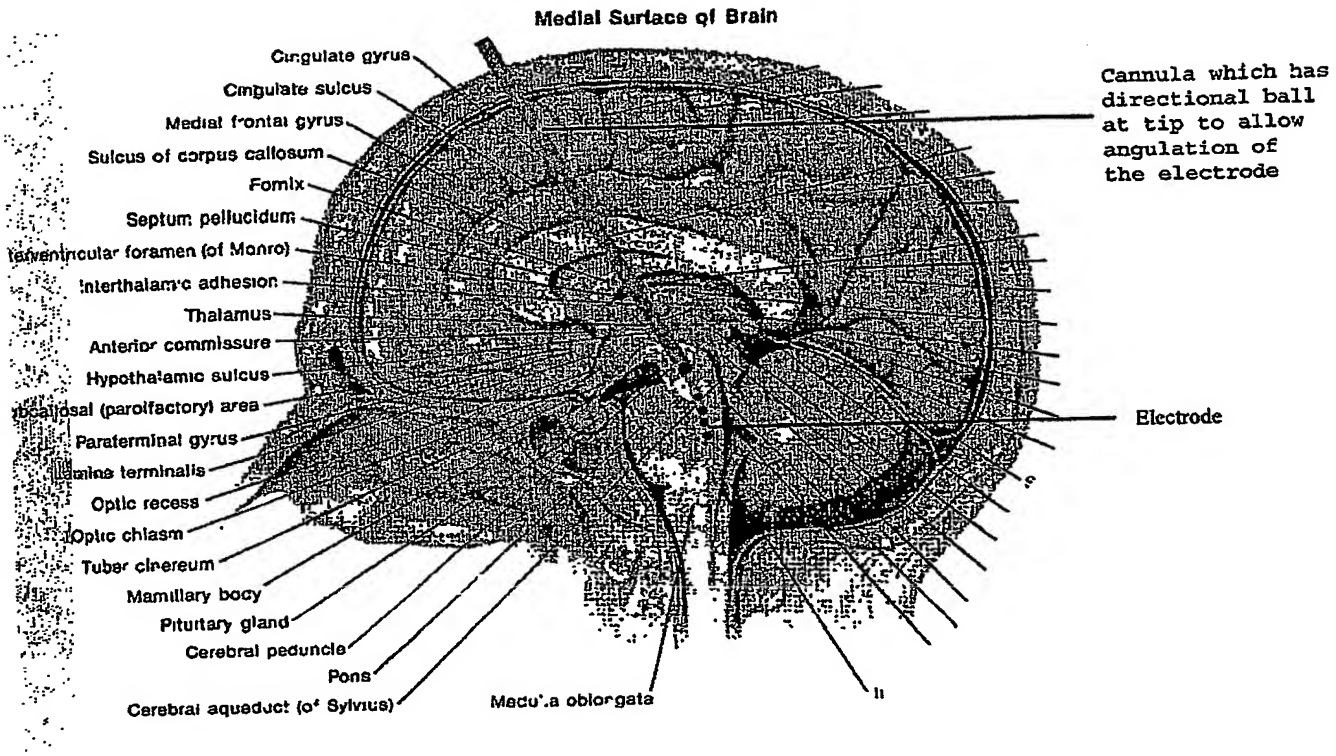


FIGURE 2



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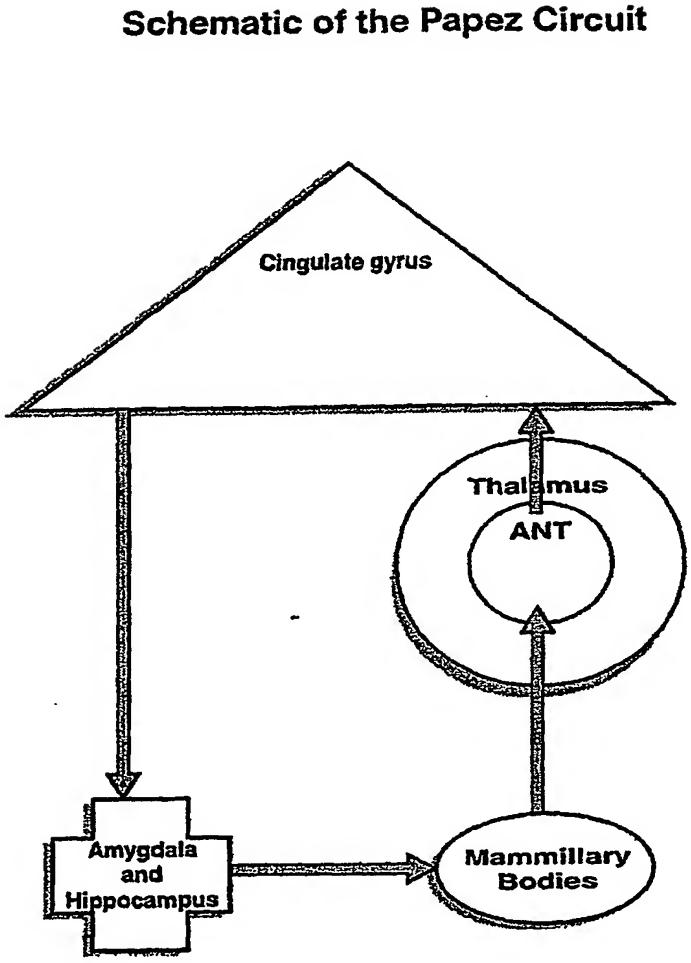
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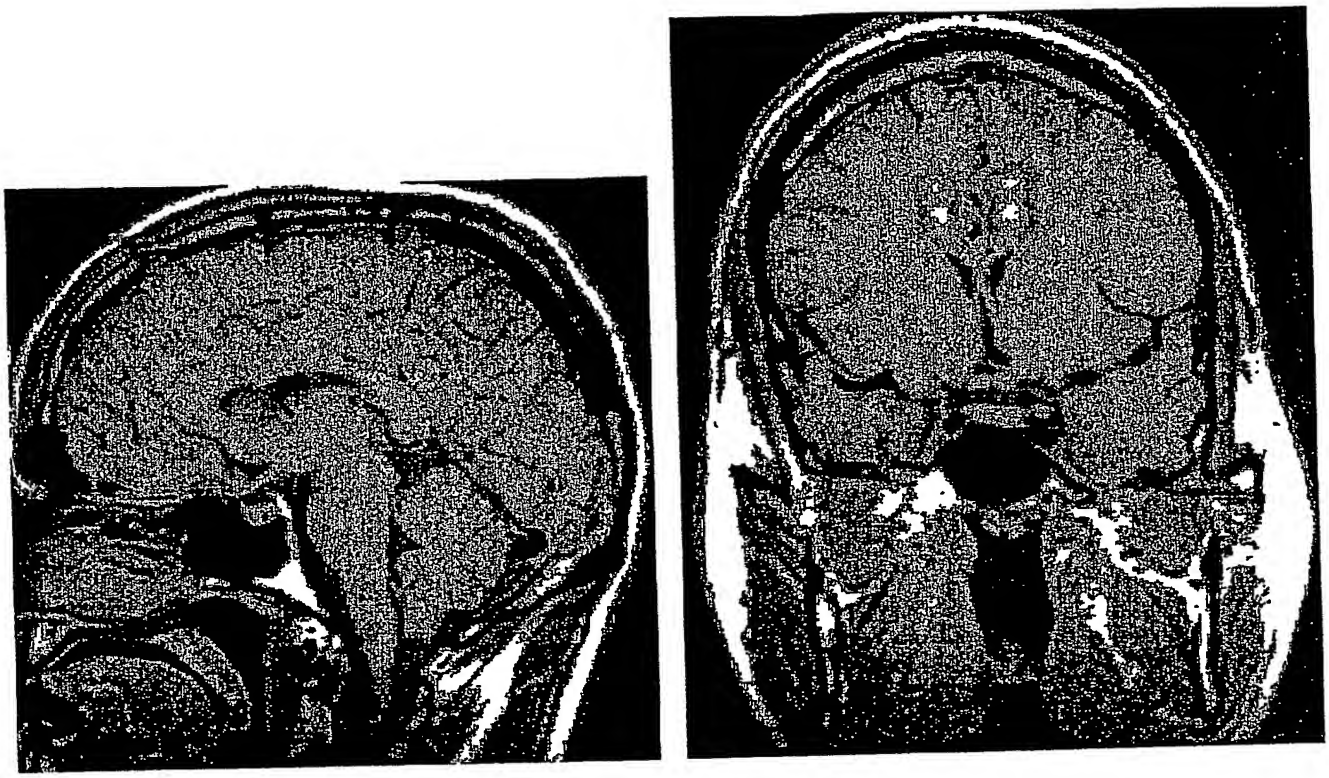
Thalamus
ANT
Amygdala and Hippocampus
Mammillary Bodies

Figure 4:



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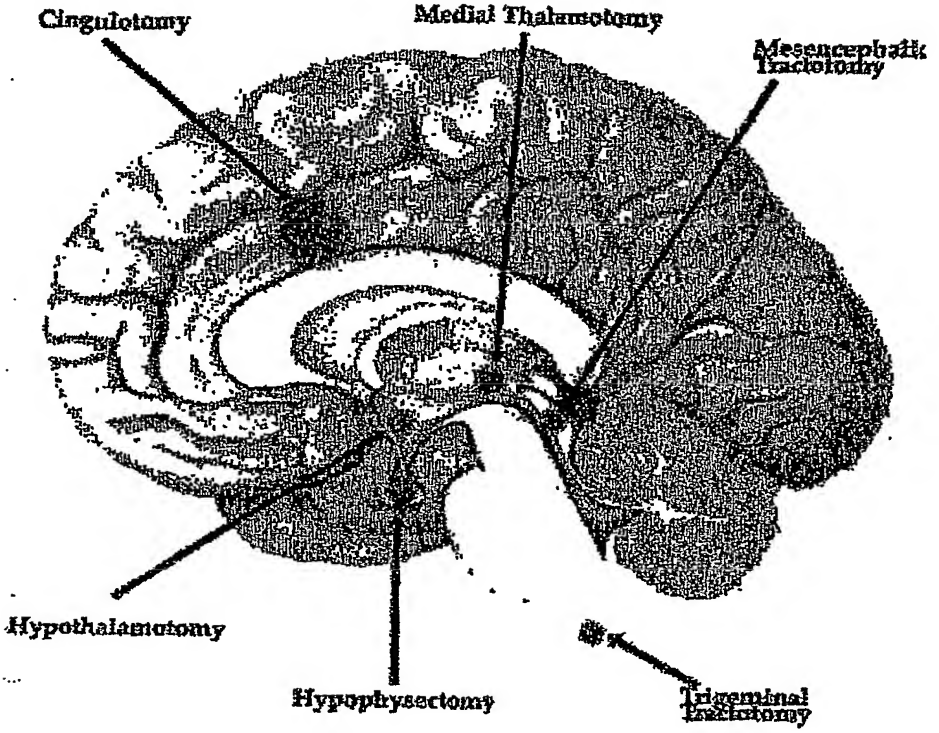

Figure 6

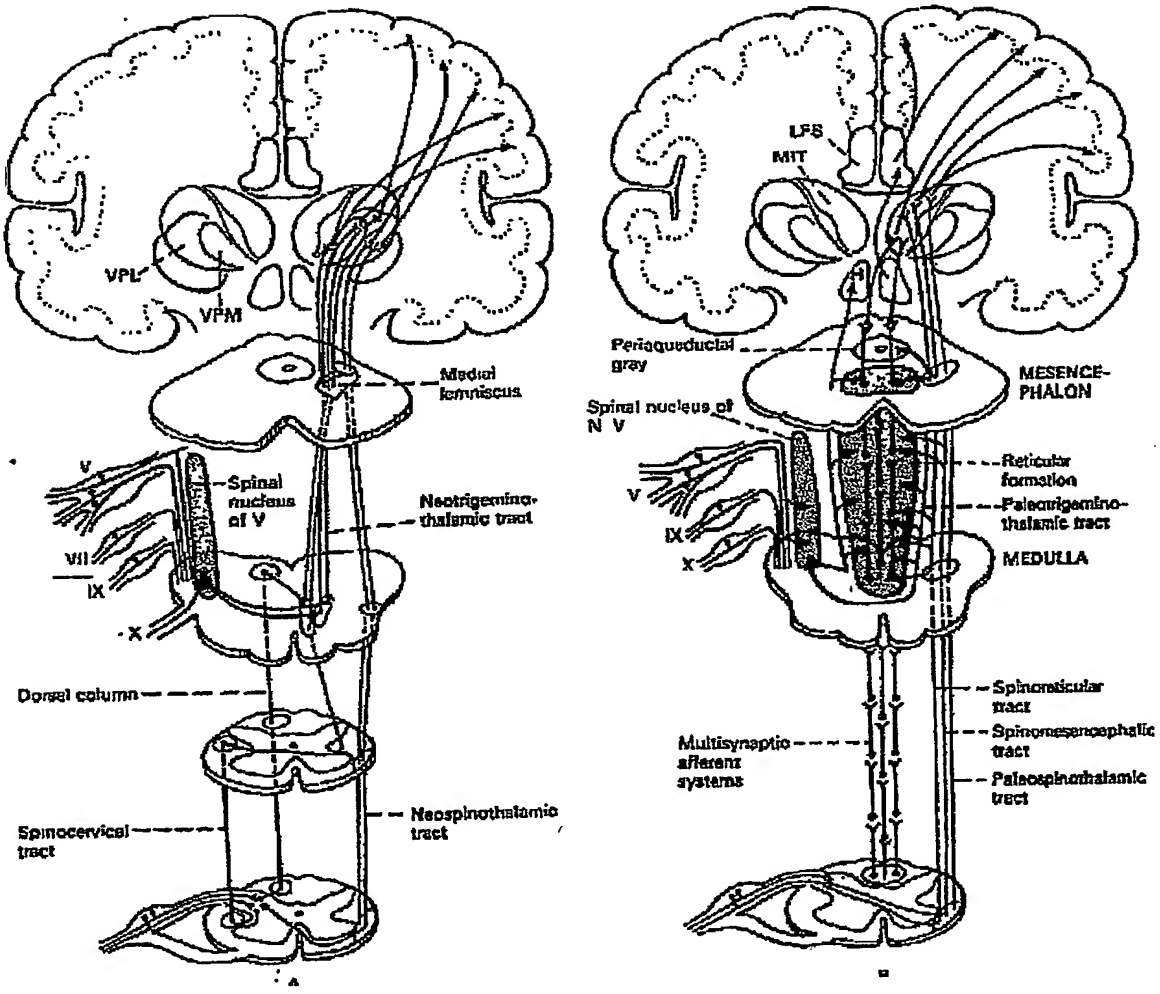

Figure 7:

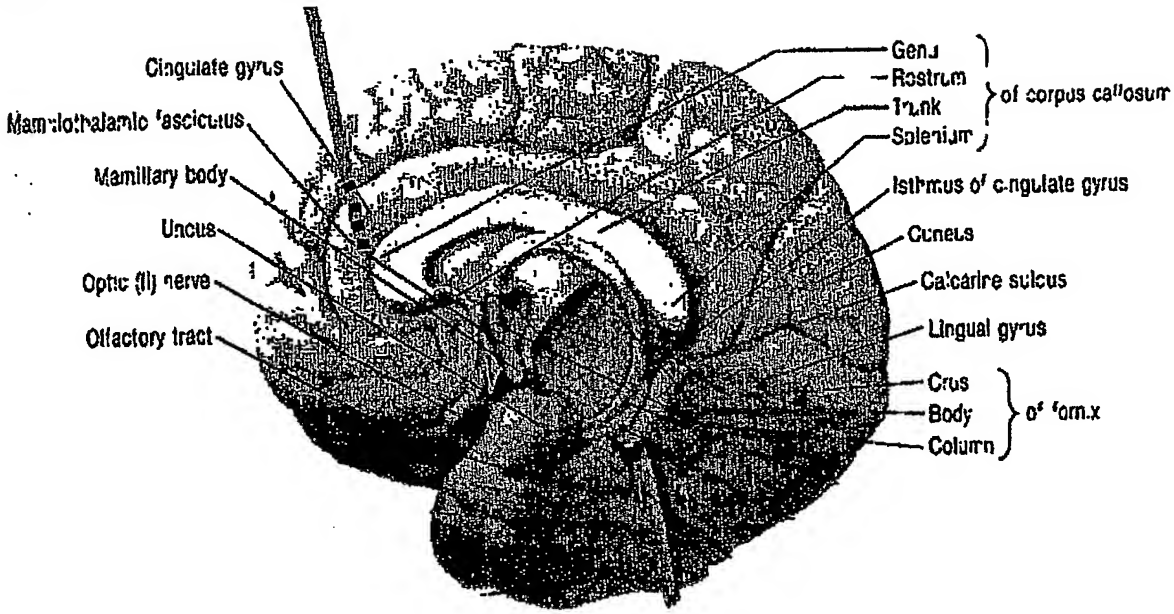

Figure 8

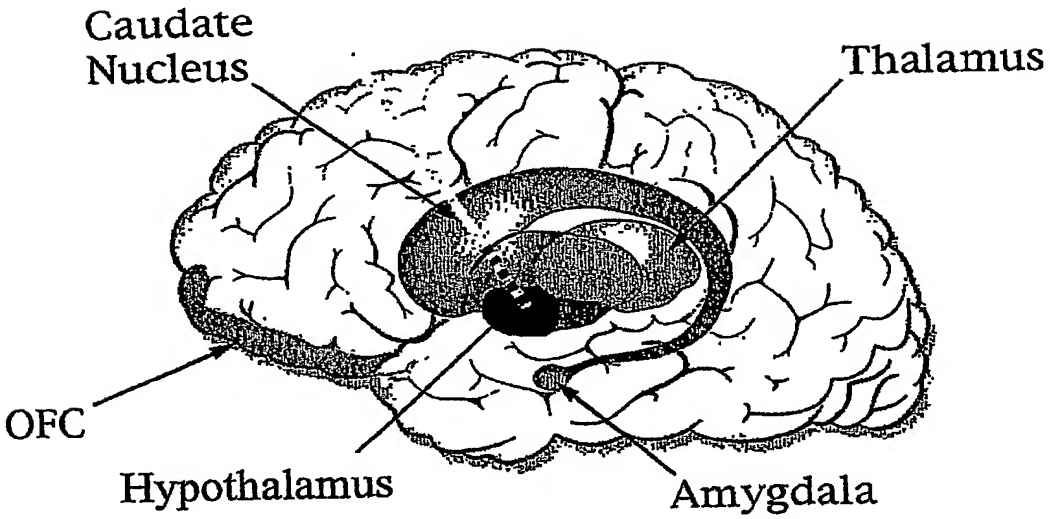

Figure 9

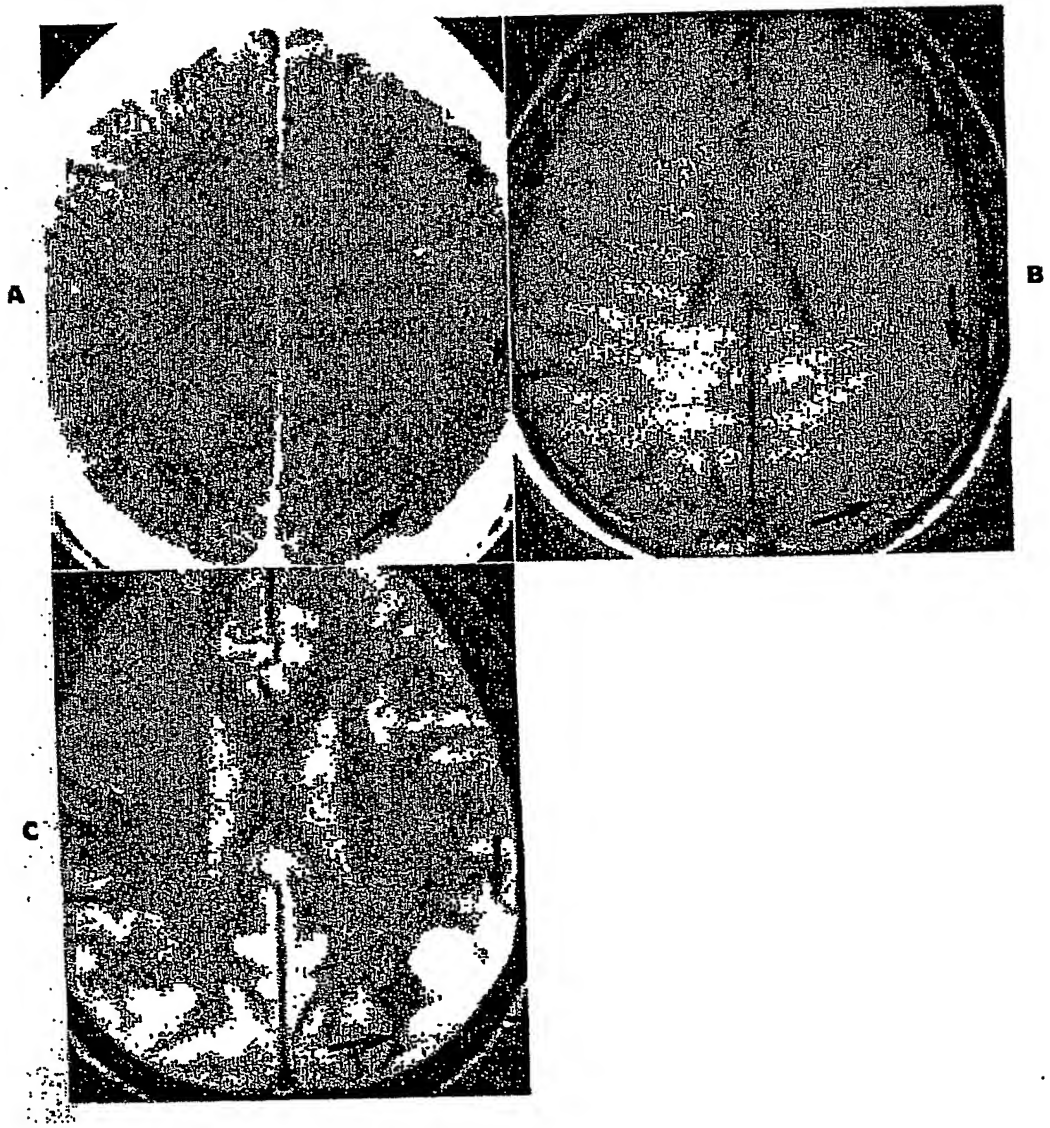

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Figure 10

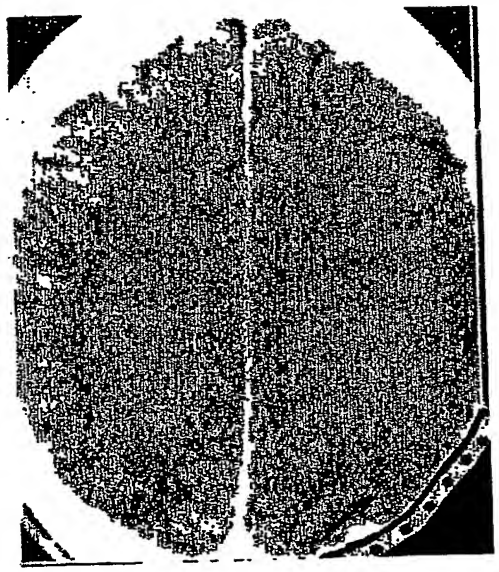

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Figure 11

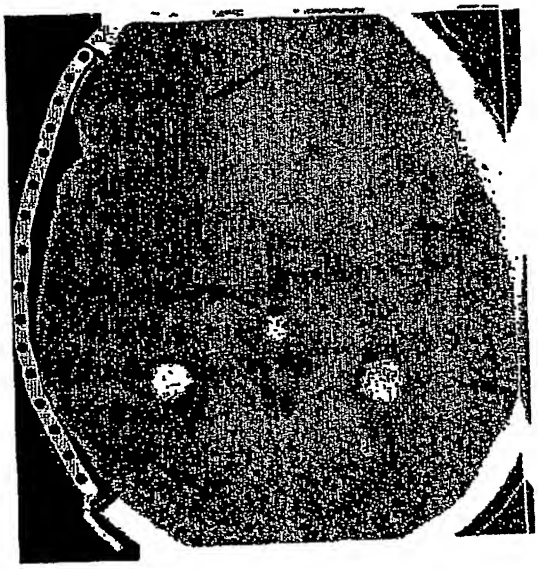

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TABLE 1

Limbic Structures

(1) Structure	Ventral-Dorsal	Medial-Lateral	Antero-Posterior
ACC	7mm from midline	20-25mm poster to tip of frontal horn	1-2mm above roof of lateral venrticle
		10-25mm anterior to AC	
Amy	S – L 12.0-22.0 ML: 1.0 to 2.5	AP: -1.2 to -2.5	T – A 20.3 (PC)-10.9 (PC) DV: -1.2 to -2.5
Hipp			
MB	ML: 0.0 to 0.5	AP: 0.2 to 1.2	DV: -0.5 to 1.2
Ant	ML: 0.2 to 1.2	AP: 0.5 to -0.5	DV: 0.2 to 1.3

ACC – Anterior Cingulate Gyrus

Amy – Amygdala

Hipp – Hippocampus

MB – Mammillary bodies

Ant – Anterior nucleus of thalamus

Insula

Table 2

Hypothalamic Hormone	Pituitary Hormone
Growth Hormone Releasing Hormone (GHRH)	Growth Hormone (GH)
Growth Hormone release-inhibiting hormone (Somatostatin)	
Prolactin releasing factor (PRF)	Prolactin (PRL)
Prolactin release-inhibiting factor (PIF - Dopamine)	
Thyrotropin-releasing hormone (TRH)	Thyrotropin (TSH)
Corticotropin- releasing hormone (CRH)	Proopiomelanocortin (POMC)
Gonadotropin- releasing hormone (GnRH)	Lueinizing hormone Follicle-stimulating hormone
Luteinizing hormone release-inhibiting factor	

(LH)	
Vasopressin Oxytocin	

Table 3

Hypothalamic Areas and Functions

Preoptic Area	Temperature regulation
Supraoptic Tract	Neurohypophyseal tract – oxytocin, vasopressin(also effects memory)
Paraventricular nuclei	Neurohypophyseal tract
Suprachiasmatic nucleus	Diurnal/Seasonal effects on pineal function
Ventromedial nucleus	Orbital cortex of frontal lobe
	Amygdaloid complex
	Hyperphagia with stimulation
Dorsal medial	Savage behavior
Periventricular nuclei	Thalamic connections
Hypothalmohypophyseal region	
Lateral hypothalamus	Agresssion and Autonomic function
Dorsal and Lateral	Anger

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☐ ***Scanned copy is best available.*** Some drawings are dark.